Effects of Chronic Iodine Administration on Thyroid Status in Euthyroid Subjects Previously Treated with Antithyroid Drugs for Graves’ Hyperthyroidism*

ELIO ROTI, ELIANA GARDINI†, ROBERTA MINELLI†, LINA BIANCONI, MARIO SALVI, GILBERTO GAVARUZZI, AND LEWIS E. BRAVERMAN

Centro per lo Studio, Prevenzione, Diagnosi e Curat della Tiroeatie, Cattedra di Endocrinologia, Università di Parma, and Servizio di Medicina Nucleare, Ospedali Riuniti di Parma, Parma, Italy; and the Division of Endocrinology and Metabolism, University of Massachusetts Medical School, Worcester, Massachusetts 01655

ABSTRACT

In view of the adverse effects of the administration of pharmacological quantities of iodine to euthyroid patients with a history of a wide variety of thyroid disorders, it has been suggested that iodine-containing medications and radiopaque dyes containing iodine should be avoided, if possible, in patients with underlying thyroid disease. We have now prospectively studied the effects of pharmacological doses of a saturated solution of potassium iodide (SSKI) on thyroid function in euthyroid patients with a previous history of hyperthyroid Graves’ disease successfully treated with antithyroid drugs. Ten euthyroid women (mean age, 56 yr) who had hyperthyroid Graves’ disease successfully treated with methimazole 38.4 ± 4.7 months earlier were evaluated before, during, and after the administration of 10 drops SSKI daily for 90 days. The following thyroid function tests were obtained: serum T4, T3, TSH, TSH receptor antibody (TSH-RAb), and anti-thyroid peroxidase antibody (AbTPO) concentrations; TRH tests; and iodine perchlorate discharge tests. Serum T4, T3, basal and TRH-stimulated TSH, and TSH-RAb values were normal before SSKI administration, but serum AbTPO levels were markedly positive in 7 and iodine perchlorate discharge tests were positive in 4 of these 10 women. During SSKI administration, basal and TRH-stimulated serum TSH values increased above normal in 2 women with normal serum T4 and T3 concentrations; thyroid hormone values and TRH tests were normal in the other 8 patients and similar to values observed in 4 euthyroid women without a history of thyroid disease given SSKI. Serum AbTPO increased slightly, but significantly, during SSKI administration in the 7 women with positive values at baseline (P < 0.05). TSH-RAb remained undetectable. After SSKI withdrawal, the 10 women were reevaluated 60 and 120 days later. Two women developed a blunted TSH response to TRH, but normal serum T4, T3 concentrations, and 2 women developed overt hyperthyroidism, with undetectable basal and TRH-stimulated serum TSH and elevated serum T4 and T3 concentrations, requiring methimazole therapy. All values in the remaining 6 women were similar to those present before SSKI administration. These results suggest that some euthyroid patients with a history of antithyroid drug therapy for Graves’ disease may develop thyroid dysfunction during and after excess iodine administration. The development of subclinical hypothyroidism during SSKI administration was not clinically important, but the occurrence of overt hyperthyroidism after SSKI was discontinued did require antithyroid drug therapy. It is advisable, therefore, to avoid iodine-containing substances in euthyroid patients with a history of antithyroid drug therapy for Graves’ disease. (J Clin Endocrinol Metab 76: 928-932, 1993)

IODINE-induced hyperthyroidism has been observed in patients with euthyroid nodular goiter, patients with subclinical Graves’ disease, and subjects without any apparent thyroid disease (1, 2). In the patients with subclinical Graves’ disease, iodine administration and an increase in dietary iodine intake have been reported to induce and exacerbate the hyperthyroidism (1–3). Furthermore, it has been suggested that increased dietary iodine intake is associated with an increased recurrence rate of hyperthyroidism in patients previously treated with antithyroid drugs for Graves’ disease (4, 5).

In euthyroid patients previously treated with 131I and partial thyroidectomy for Graves’ disease, iodine administration may induce hypothyroidism (6). Studies on the effects of iodine administration in euthyroid subjects previously treated with antithyroid drugs for Graves’ hyperthyroidism have yielded conflicting results (7, 8). In the present study, we have evaluated the effects of pharmacological amounts of iodine on thyroid function in euthyroid subjects previously treated with methimazole (MMI) for hyperthyroid Graves’ disease.

Materials and Methods

Ten women (mean age, 56 ± 2.5 yr) who had Graves’ disease treated with MMI for 19.3 ± 2.9 months (range, 8–38 months) were enrolled in the present study after informed consent was obtained. The mean daily dose of MMI was 5 mg. These subjects had been euthyroid for 36.4 ± 4.7 months after MMI was discontinued before entering the present study.

Before iodide administration, thyroid status was evaluated clinically and by thyroid function tests (serum T4, T3, and basal and TRH-stimulated TSH concentrations). The 10 women were euthyroid (EG).
Five patients had grade I goiter, and 5 had grade II goiter according to WHO criteria. Circulating antithyroid peroxidase antibodies (AbTPO) and TSH receptor antibodies (TSH-RAb) were measured. The TSH assay is an immunoradiometric assay employing a monoclonal antibody labeled with $^{125}$I which binds to a unique site on the TSH molecule. A second monoclonal antibody linked to fluorescein binds on the TSH molecule, forming a sandwich. After incubation, antithyroid peroxidase coupled to a magnetic solid phase is added in excess. This binds to the TSH-monomonal antibody complex and is sedimented in a magnetic field.

An iodide perchorlate ($^{131}$I) discharge test was carried out in the 10 EG subjects. A tracer dose of $^{131}$I (5 μCi) was administered orally with 500 μg stable I at zero time. Three hours later, thyroid $^{131}$I uptake was measured, followed by the oral administration of 1 g potassium perchlorate (KCIO$_4$). The thyroid $^{131}$I uptake test was repeated 1 h after KCIO$_4$ administration. An abnormal test was defined as a discharge of $^{131}$I greater than 15% 1 h after KCIO$_4$ administration. A TRH test was carried out to evaluate pituitary TSH reserve. Serum samples for TSH measurement were obtained before and 20 min after the iv administration of 200 μg TRH (Ares-Serono, Milan, Italy).

After these studies were completed, 10 drops of a saturated solution of potassium iodide (SSKI; 350 mg iodide) were given daily, and serum was obtained for thyroid function tests on days 15, 30, 60, and 90 of treatment and 60 and 120 days after SSKI was withdrawn. The TRH test was repeated on the last day (day 90) of SSKI administration and 60 and 120 days later.

Serum samples were kept frozen at -20 C until the study was completed. All samples were assayed in the same assay, in duplicate, and in random order. Serum T$_4$ and T$_3$ concentrations were measured by RIA, and serum TSH by a sensitive immunoradiometric method with materials obtained from Ares-Serono. Normal ranges for serum thyroid hormone concentrations are as follows: T$_4$, 57.9-154.5 nmol/L; T$_3$, 0.92-3.07 nmol/L; TSH, 0.2-6.5 mU/L. The intraassay coefficients of variation were 1.4% for T$_4$, 3.4% for T$_3$, and 4.2% for TSH. AbTPO and TSH-RAb were measured by RIA and a radioreceptor binding assay, respectively, with materials obtained from Henning-Berlin GmbH (Berlin, Germany). Levels of serum AbTPO and TSH-RAb were considered to be positive. Urinary iodine excretion was measured in a morning urine sample by the method of Benotti et al. (9), and values of iodine excretion were calculated as micrograms per g creatinine.

I-ClO$_4$ discharge tests were carried out in 8 euthyroid women, aged 30.5 ± 2.2 yr, who had never had autoimmune thyroid disease (10). All had a normal I-ClO$_4$ discharge test. TRH tests were carried out in 4 of these women who were then given SSKI and studied over the same period of time as the 10 EG subjects.

Basal serum TSH concentrations in the EG subjects before SSKI administration were considered elevated when they exceeded the mean + 2 σ of values in the control subjects. During SSKI administration, the EG patients were considered to have elevated serum TSH concentrations when one or more serum TSH values were higher than the highest mean + 2 σ of TSH concentrations in the control subjects during SSKI administration. TRH-stimulated serum TSH concentrations in EG subjects were considered elevated when they were higher than the corresponding mean + 2 σ of values in control subjects (11). EG subjects were considered to have iodine-induced subclinical hypothyroidism when basal and/or TRH-stimulated serum TSH concentrations during SSKI administration were elevated. Basal and TRH-stimulated serum TSH concentrations were considered suppressed when they were lower than 0.2 mU/L.

Statistical analysis was carried out by paired and unpaired Student's $t$ tests to compare thyroid function tests before and after SSKI administration and the TSH response to TRH at baseline, on day 60 of SSKI administration, and 60 and 120 days after SSKI was withdrawn, in the same group and between the groups; one-way analysis of variance (1 way ANOVA) was used to evaluate hormone patterns in EG and control subjects during SSKI administration, and Fisher's exact test was employed to evaluate the prevalence of abnormal tests in different groups. All values are reported as the mean ± se, except when otherwise indicated.

### Results

#### Thyroid status before SSKI administration (baseline)

Serum T$_4$, T$_3$, and basal and TRH-stimulated TSH concentrations in the EG subjects were similar to those observed in control subjects (Table 1). Furthermore, none of the EG subjects had elevated or suppressed serum TSH responses to TRH.

<table>
<thead>
<tr>
<th></th>
<th>EG (n = 10)</th>
<th>Controls (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T$_4$ (nmol/L)</td>
<td>111.3 ± 6.4</td>
<td>96.5 ± 15.8</td>
</tr>
<tr>
<td>T$_3$ (nmol/L)</td>
<td>1.9 ± 0.1</td>
<td>1.8 ± 0.2</td>
</tr>
<tr>
<td>Basal TSH (mU/L)</td>
<td>1.2 ± 0.2</td>
<td>1.5 ± 0.5</td>
</tr>
<tr>
<td>20 min TSH responses to TRH (mU/L)</td>
<td>10.7 ± 2.4</td>
<td>13.5 ± 3.3</td>
</tr>
</tbody>
</table>

The number of subjects in each group is in parentheses. Values are the mean ± se. No significant difference was observed in thyroid function tests between EG and control subjects. None of the EG subjects had elevated or suppressed basal and TRH-stimulated serum TSH concentrations.
The other eight EG subjects had a slight increase in basal serum TSH concentrations during SSKI administration, reaching the highest value on day 60 (3.9 ± 1.4 mU/L; P < 0.01, by 1 way ANOVA). In these eight EG subjects, the TSH response to TRH on day 90 was 21.9 ± 4.3 mU/L, significantly higher than that observed before SSKI administration (P < 0.01, by Student's t test), but not different from values in the control subjects on day 90. During SSKI administration, no EG patient had suppressed basal and TRH-stimulated TSH concentrations.

In the eight euthyroid EG subjects, serum T4 concentrations did not change during SSKI administration, whereas serum T3 concentrations showed a significant increase, reaching the highest value on day 90 (2.1 ± 0.1 nmol/L; P < 0.05, by 1 way ANOVA). However, none of these subjects had serum T3 concentrations above the upper limit of normal.

In the seven AbTPO-positive EG subjects, the antibody levels slightly, but significantly, increased (P < 0.05, by 1 way ANOVA) during SSKI administration, reaching a peak of 5478 ± 2437 UI/ml on day 90. Serum TSH-RAb remained undetectable during SSKI administration. Serum AbTPO and TSH-RAb remained undetectable in the control women.

**Thyroid status after SSKI**

SSKI was discontinued after day 90, and all subjects were reevaluated 60 and 120 days later. Serum TSH was undetectable on day 60 and did not increase after TRH in one EG patient (Table 3). The TSH response to TRH was blunted in two others. The two EG women who had elevated basal or TRH-stimulated serum TSH concentrations during SSKI administration had serum basal and TRH-stimulated TSH values similar to those observed before SSKI was administered. The remaining five EG subjects had basal and TRH-stimulated serum TSH concentrations similar to those observed before SSKI administration. The EG subject with undetectable serum TSH and no TSH response to TRH had serum T4 and T3 concentrations above the upper limit of normal (230 and 3.95 nmol/L, respectively; Table 3), was clinically hyperthyroid, and was treated with MMI. The two EG patients with a blunted TSH response to TRH had serum T4 and T3 concentrations within the normal range. These two subjects did not have any signs or symptoms of hyperthyroidism.

One hundred and twenty days after SSKI was discontinued, a second EG patient had an undetectable serum TSH concentration and no TSH response to TRH and had elevated serum T4 and T3 concentrations of 234.3 and 4.3 nmol/L, respectively (Table 3). This patient was clinically hyperthyroid and was also treated with MMI. The two EG subjects who had a blunted TSH response to TRH continued to have a reduced TSH response, had serum T4 and T3 concentrations within the normal range, and had no signs or symptoms of hyperthyroidism. Thus, by 120 days after SSKI was discontinued, two patients who had developed hyperthyroidism, two patients had a blunted TSH response to TRH but remained euthyroid, and six patients remained euthyroid with normal basal and TRH-stimulated serum TSH values.

The 24-h thyroid 123I uptakes in the two hyperthyroid patients during MMI treatment were 37% and 49%, respectively.

Thyroid function tests in the six EG patients who did not develop thyroid dysfunction and in the four control women before, during, and after SSKI administration are reported in Table 4.

After SSKI was discontinued, serum TSH-RAb remained undetectable in all control and EG subjects, including the two EG patients who developed hyperthyroidism.

**Discussion**

In previous studies, it has been suggested that iodine-induced hyperthyroidism may occur in subjects with subclinical Graves' disease (1). Subjects residing in an endemic iodine-deficient goiter area with positive circulating long-acting thyroid stimulator or long-acting thyroid stimulator protector developed hyperthyroidism during iodine prophylaxis, suggesting that Graves' hyperthyroidism was not pre-
Mone concentrations rapidly rebounded to elevated values during iodine administration, but serum thyroid hormone concentrations during the continued administration of iodine. We have observed that iodine administration to patients with hyperthyroid Graves' disease decreased serum thyroid hormone concentrations and during the administration of large amounts of iodine. However, two patients with MM1 did not develop hyperthyroidism during the administration of small quantities of iodine (20 μg/day) to euthyroid subjects immediately or 6 months after antithyroid drugs were discontinued in patients with Graves' disease induced a small increase in the serum protein-bound iodide content due to enhanced trapping of iodine (17). Patients with T3 toxicity due to latent Graves' disease may also develop overt hyperthyroidism after iodine administration (13). Furthermore, it has been suggested that increased dietary iodine intake was associated with an increased recurrence rate of Graves' hyperthyroidism (4, 5). In a prospective study, the administration of small quantities of iodine (200 μg/day) to euthyroid subjects immediately or 6 months after antithyroid drugs were discontinued in patients with Graves' disease induced a small increase in the serum protein-bound iodide concentration and an increased recurrence rate of clinical hyperthyroidism (7). However, in another study, Thalassinos and Fraser (8) reported that the administration of 10 mg iodine daily to euthyroid subjects previously treated with antithyroid drugs for Graves' disease did not increase the recurrence rate of hyperthyroidism. Patients thyroidectomized for Graves' disease who resided in an area with an elevated iodine intake had a higher recurrence rate of hyperthyroidism than patients residing in an area with a low iodine intake (14). Finally, antithyroid drugs were less effective in controlling the hyperthyroidism of patients residing in a region with adequate iodine intake than in patients living in an area of low iodine intake (15).

In the present study, we observed that euthyroid subjects with a previous episode of Graves' hyperthyroidism treated with MMI did not develop hyperthyroidism during the administration of large amounts of iodine. However, two patients developed hyperthyroidism after SSKI was discontinued. Vagenakis et al. (16) observed that subjects with nontoxic nodular goiter treated with pharmacological amounts of SSKI developed mild hyperthyroidism, which became far worse after iodine was discontinued. Emerson et al. (17) observed that iodine administration to patients with hyperthyroid Graves' disease decreased serum thyroid hormone concentrations, although a rebound increase was observed during the continued administration of iodine. We have previously observed that patients with hyperthyroid Graves' disease had normal serum thyroid hormone concentrations during iodine administration, but that serum thyroid hormone concentrations rapidly rebounded to elevated values after iodine was discontinued (18). In a single patient with iodine-induced hyperthyroidism, further iodine administration resulted in an amelioration of the hyperthyroidism (19). These findings suggest that the effects of iodine on thyroid function in patients with active or potential hyperthyroidism are probably due to at least two mechanisms. First, excess iodine partially decreases thyroid hormone release from the gland, especially in patients with hyperthyroidism (20), thus partially explaining the transient improvement during iodine therapy in hyperthyroid patients. Second, iodine administration may result in continued and even excessive synthesis of thyroid hormones, especially in areas of decreased iodine intake or in thyroid glands with diffuse or nodular autonomy.

In the two EG patients who developed hyperthyroidism after SSKI was discontinued, serum TSH-RAb were not present before, during, and after iodine administration. This finding does not exclude the diagnosis of recurrent Graves' disease, since it has been reported that not all patients with Graves' disease have TSH-RAb (21). It is unlikely that these two EG patients had autonomous thyroid function before and during SSKI administration, since basal and TRH-stimulated serum TSH concentrations were normal. Others have observed local inflammatory lesions in the thyroids from patients with iodine-induced hyperthyroidism, suggesting a destructive process with leakage of thyroid hormones into the blood (22). We did not observe any signs or symptoms suggesting subacute thyroiditis in the two EG patients who developed hyperthyroidism after iodine withdrawal. Thus, in the two EG subjects who developed hyperthyroidism after iodine withdrawal, the onset of hyperthyroidism may have been due to increased synthesis of thyroid hormone and partial inhibition of hormone release during iodine administration, with a subsequent release of stored hormone after iodine withdrawal. It is also possible that these two patients might have developed spontaneous recurrent hyperthyroidism regardless of iodine administration.

A positive I-131 discharge test is a marker of an intrathyroid iodine organization defect and subsequent decreased hormone synthesis (23, 24), but may also be due to an increased intrathyroid iodide content due to enhanced trap-

---

**TABLE 4.** Serum T4, T3, and basal and TRH-stimulated serum TSH concentrations before, during, and after SSKI administration in six EG subjects who remained euthyroid during and after SSKI administration and in the four control women (C).

<table>
<thead>
<tr>
<th></th>
<th>Days on SSKI</th>
<th>Days after SSKI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>T4 (nmol/L)</td>
<td></td>
<td>EG</td>
</tr>
<tr>
<td></td>
<td>105 ± 9</td>
<td>102 ± 8</td>
</tr>
<tr>
<td></td>
<td>96 ± 16</td>
<td>93 ± 7</td>
</tr>
<tr>
<td>T3 (nmol/L)</td>
<td></td>
<td>EG</td>
</tr>
<tr>
<td></td>
<td>1.9 ± 0.1</td>
<td>1.8 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>1.8 ± 0.2</td>
<td>2.1 ± 0.2</td>
</tr>
<tr>
<td>TSH (mU/L)</td>
<td></td>
<td>EG</td>
</tr>
<tr>
<td></td>
<td>0.9 ± 0.2</td>
<td>2.7 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>1.5 ± 0.5</td>
<td>3.3 ± 1.3</td>
</tr>
<tr>
<td>20 min TSH response to TRH (mU/L)</td>
<td></td>
<td>EG</td>
</tr>
<tr>
<td></td>
<td>7.5 ± 1.1</td>
<td>21.5 ± 3.5</td>
</tr>
<tr>
<td></td>
<td>13.5 ± 3.9</td>
<td>21.8 ± 6.3</td>
</tr>
</tbody>
</table>

All values are the mean ± SE.
ping of iodide, since a large number of patients newly diagnosed with Graves’ hyperthyroidism have a positive iodine discharge test (our personal observation). In the present study, only 4 of 10 euthyroid women previously treated with MMI for hyperthyroid Graves’ disease had a positive I-ClO₄ discharge test, and only 1 developed iodine-induced subclinical hypothyroidism. The other patient who developed iodine-induced subclinical hypothyroidism had a negative I-ClO₄ discharge test. This is in contrast to the high prevalence of iodine-induced hypothyroidism and positive I-ClO₄ discharge tests in euthyroid patients previously treated for active Graves’ disease with definitive therapy, such as radioactive iodine and subtotal thyroidectomy (6); in euthyroid patients with a history of amiodarone-induced thyrotoxicosis (27); and in euthyroid patients with a previous lobectomy for uninodular goiter (28).

In conclusion, it is probably advisable to avoid administering pharmacological quantities of iodine to euthyroid patients with a history of antithyroid drug therapy for hyperthyroid Graves’ disease, since it is not possible to predict which patient will develop iodine induced hyper- or hypothyroidism.

Acknowledgment

We thank Mr. Luigi Guerra for his excellent technical assistance.

References